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Outcomes after endoscopic retrograde cholangiopancreatography with general anaesthesia *versus* sedation

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Abstract

Background: We tested the primary hypothesis that use of general anaesthesia *vs* sedation increases vulnerability to adverse discharge (in-hospital mortality or new discharge to a nursing facility) after endoscopic retrograde cholangiopancreatography (ERCP).

Methods: In this retrospective cohort study, adult patients undergoing ERCP with general anaesthesia or sedation at a tertiary care hospital were included. We calculated adjusted absolute risk differences between patients receiving general anaesthesia *vs* sedation using provider preference-based instrumental variable analysis. We also used mediation analysis to determine whether intraoperative hypotension during general anaesthesia mediated its effect on adverse discharge.

Results: Among 17 538 patients undergoing ERCP from 2007 through 2018, 16 238 received sedation and 1300 received GA. Rates of adverse discharge were 5.8% (n=938) after sedation and 16.2% (n=210) after general anaesthesia. Providers' adjusted mean predicted probabilities of using general anaesthesia for ERCP ranged from 0.2% to 63.2% of individual caseloads. Utilising provider-related variability in the use of general anaesthesia for instrumental variable analysis resulted in an 8.6% risk increase (95% confidence interval, 4.5–12.6%; P<0.001) in adverse discharge among patients receiving general anaesthesia *vs* sedation. Intraoperative hypotensive events occurred more often during general anaesthesia and mediated 23.8% (95% confidence interval, 3.9–43.7%: P=0.019) of the primary association.

Conclusions: These results suggest that use of sedation during ERCP facilitates reduced adverse discharge for patients for whom general anaesthesia is not clearly indicated. Intraoperative hypotension during general anaesthesia for ERCP partly mediates the increased vulnerability to adverse discharge.

Keywords: endoscopy; ERCP; general anaesthesia; hypotension; instrumental variable analysis; mediation analysis; monitoring; outcomes research; provider variability; sedation

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Editor's key points

- Clinicians have to make difficult decisions based on biological plausibility, clinical experience, the body of evidence, balancing benefit *vs* harm, and finally applying all of this to individual patients.
- One of the challenging decisions for anaesthetists is whether to choose sedation or general anaesthesia with tracheal intubation for patients undergoing endoscopic retrograde cholangiopancreatography.
- The theoretical benefits of general anaesthesia with intubation are airway protection from aspiration and control of ventilation, but the potential risks include haemodynamic compromise and prolonged recovery.
- This large retrospective study suggests that the risks of general anaesthesia with intubation might outweigh the benefits, with many patients experiencing hypotension during general anaesthesia, with a markedly increased risk of adverse post-procedural outcomes.

Endoscopic retrograde cholangiopancreatography (ERCP) carries an increased risk of pancreatitis, bleeding, perforation, and infection.[1] The presence of an anaesthesiologist during ERCP may improve procedural efficacy and safety because of deeper sedation,[2] immediate management of respiratory and haemodynamic complications,[3,4] and faster recovery.[5] In recent years, the frequency of anaesthesia provider-administered sedation for endoscopies has increased substantially.[3,6,7] Both sedation and general anaesthesia (GA) with intubation have specific complication risks, including aspiration, hypoxaemia, and hypotension.[3] However, there is currently no established standard of anaesthesia care for ERCP.

In the USA, approximately 600 000 ERCPs are performed anually.[8] Data evaluating the impact of anaesthesia type on ERCP outcomes are limited. A recent study reported higher rates of adverse events in patients who received sedation over GA for ERCP.[9] However, outcomes of interest were sedation-related adverse events including hypoxaemia and the need for airway manoeuvres such as chin lift or jaw thrust. We argue that brief desaturations may not be indicative of a poor outcome but are expected to occur more frequently during sedation. It remains unclear whether sedation-related adverse events contribute to long-term morbidity and mortality after ERCP.

We performed an instrumental variable analysis to test the hypothesis that use of GA *vs* sedation increases the vulnerability to adverse discharge after ERCP. We then tested the secondary hypothesis that intraoperative sedation-related adverse events such as hypotension mediate the effect of anaesthesia type on adverse discharge.

Methods

Study design

This study was reviewed by the Committee on Clinical Investigations, which determined that the study meets criteria for exempt status (2019P000556). The requirement for written informed consent was waived. Data were obtained for patients undergoing ERCP under GA with intubation or sedation between January 2007 and December 2018 at Beth Israel Deaconess Medical Center in Boston, MA, USA. Data were collected from hospital-registry databases (Supplement 1, section 1.1). This manuscript adheres to STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) guidelines (Supplement 2).

Study cohort

We included patients aged 18 yr or older who had an ASA physical status below 6. **Current Procedural Terminology (CPT) codes were used** to identify ERCP procedures (Supplement 1 and Table S1). The study exposure was use of GA with a tracheal intubation event (not later than 5 min within procedure start) *vs* use of sedation (monitored anaesthesia care [MAC]). Sedation cases that were converted to GA during the procedure were assigned to the sedation group. Details on the exposure are provided in Supplement 1, section 1.2. Cases that were missing data required for analyses were excluded. All included ERCPs were managed by anaesthesia providers who had performed a minimum of 50 anaesthetics during the study period. Details on the primary anaesthesiologist for each case are provided in Supplement 1, section 2.1.

Primary analysis

The primary outcome was adverse discharge, defined as in-hospital mortality or discharge of previously home-dwelling patients to a skilled nursing or healthcare facility, as opposed to routine discharge to home or an inpatient rehabilitation facility. We *a priori* defined a large number of patient, procedure, and anaesthesia-related covariates based on risk factors of adverse discharge,[10] high-risk endoscopy, and factors used by clinicians to plan the anaesthesia type (Supplement 1, section 1.3 and Table S2).

We calculated adjusted absolute risk differences (aRD) and 95% confidence intervals (CI) in adverse discharge between GA *vs* sedation groups using instrumental variable analysis. Instrumental variable analysis attempts to exploit observational settings where patients are randomly assigned to study groups by a naturally varying factor.[11,12] It requires an instrument which affects the exposure (whether a patient is more or less likely to receive GA *vs* sedation), but is unrelated to the outcome (adverse discharge) except for its effect on the intervention. We assessed the proportion of GA use among anaesthesiologists, which could range from 0% to 100% of their own ERCP caseload (Supplement 1 and Figure S2). We chose the anaesthesiologist's preference for the use of GA *vs* sedation during ERCP as the instrument. Using provider-attributable preference as an instrument derives from the assumption that a patient admitted to the hospital is randomly assigned to their anaesthesiologist, who in turn will have a higher or lower probability of using GA. However, these provider preferences are unlikely to be associated with changes in adverse discharge disposition. Details on development and assessment of the instrument are described in Supplement 1, section 2.

We estimated a multivariable-adjusted two-stage instrumental variable binomial probit model comparing GA *vs* sedation groups. The first stage model predicted the use of GA based on the dichotomised instrumental variable (cases performed by providers with a low preference [<50th percent rank] *vs* cases performed by providers with a high preference [>50th percent rank] for using GA *vs* sedation) and all covariates. In the second stage, the outcome model for adverse

discharge was estimated based on the predicted values of GA use from the first-stage model as exposure and the covariates (Supplement 1 and Table S2). Adjusted aRD and 95% CI from the instrumental variable model were calculated by transforming the estimated coefficients to the probability scale using the standard normal distribution in 500 bootstrap samples. Patient characteristics across groups of the dichotomised instrument are shown in Supplement 1 and Table S3. To assess balance of confounding variables across instrument groups, we estimated standardised differences with a cut-off of >0.1 to define a significant difference (Table S3).[11] To test for instrument strength, we reported Wald *F*-statistics from the first-stage instrumental variable models with an *F*-value >10 indicating a strong instrument.[13]

Key secondary analysis

We used path mediation analysis to determine whether intraoperative sedation-related adverse events were mediators of the association between GA or sedation and adverse discharge. We tested respiratory sedation-related adverse events (intraoperative hypoxaemia event of SpO_2 <90%) and cardiovascular sedation-related adverse events (intraoperative hypotensive event of MAP <55 mm Hg/MAP <65 mm Hg,[14] use of vasopressors, or both) as potential mediator candidates, respectively (Supplement 1, section 3.1). We first determined whether risks of sedation-related adverse events differed between patients receiving GA *vs* sedation using logistic regression (Supplement 1, section 3.2). Subsequently, we tested whether respiratory and cardiovascular sedation-related adverse events were associated with the primary outcome of adverse discharge, respectively, indicating possible effect mediation (Supplement 1, section 3.3).

Conditional on an association with adverse discharge, we proceeded using the mediator candidate in adjusted formal mediation analysis based on the method described by Buis (Fig. 1).[15] We estimated odds ratios of the indirect (mediated) effect of sedation-related adverse events and the total (unmediated) effect of GA use on adverse discharge using 500 bootstrap samples.[16] Models were adjusted for all covariates of the primary analysis. Percentage mediation by sedation-related adverse events was calculated by the formula: (ln[indirect effect]/ln[total effect])×100.[16] In addition, we applied more rigorous definitions of the mediator variables requiring a minimum duration of 3 min of measured sedation-related adverse events.

Sensitivity analyses

Propensity score matching

We performed propensity score matching to further address the possibility of unbalanced confounding between the groups (Supplement 1, section 4.1). In this cohort, we used regression analyses to compare outcomes between GA and sedation adjusting for covariates with a standardised difference of ≥0.1.[17]

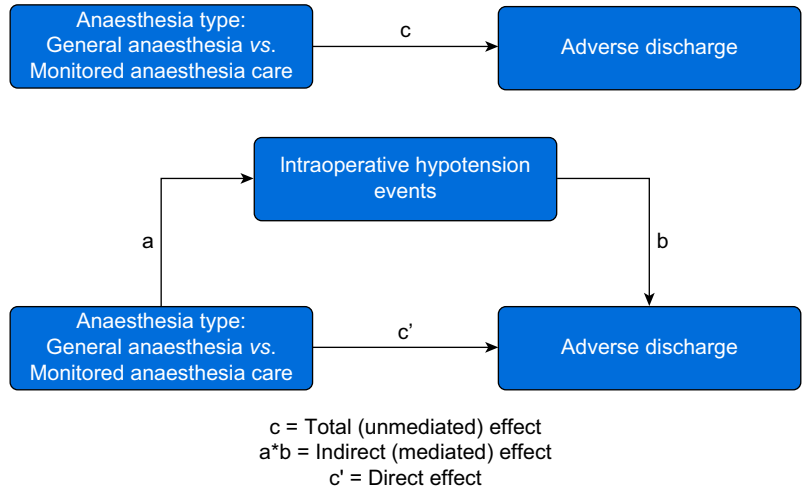

Fig 1. Path mediation analysis diagram based on the method described by Buis.[15] The total effect of anaesthesia type (GA *vs* sedation/monitored anaesthesia care) during ERCP on adverse discharge is displayed in the top diagram. The total (unmediated) effect compares odds for adverse discharge if everyone had received GA *vs* odds for adverse discharge if everyone had received sedation. The mediated effect of the primary association through cardiovascular sedation-related adverse events is displayed in the bottom diagram. The indirect (mediated) effect assumes that every patient received GA, and compares odds for adverse discharge when rates of cardiovascular sedation-related adverse events then change from the value during GA to the one during sedation. The indirect effect represents the mediated proportion of the total effect, indicating if and to which extent the effect of GA use on adverse discharge was mediated through cardiovascular sedation-related adverse events. The direct effect compares odds for adverse discharge if everyone had received GA *vs* odds for adverse discharge if everyone had received sedation, thereby fixing rates of cardiovascular sedation-related adverse events to the value they would have had during sedation. GA, general anaesthesia MAC. monitored anaesthesia care; ERCP, endoscopic retrograde cholangiopancreatography.

Robustness of the primary analysis

We performed various sensitivity analyses to assess the robustness of the instrumental variable analysis as an analytic approach, such as using modified versions of the instrumental variable, addressing a potential cluster-size bias in the instrumental variable, and the residual-inclusion method.[18] Moreover, we conducted subgroup analyses and applied modified versions of the confounder model, such as adding patient-related variables that may increase the likelihood that providers choose GA over sedation (e.g. drug abuse, anxiety, patient position). Finally, we used interaction analyses to test whether risk-related factors modified the primary association: procedural duration, comorbidity burden, inpatients *vs* outpatients, emergency, and performance of sphincterotomy. Details on all sensitivity analyses are described in the Supplement 1 (sections 2.4–2.5 and 4; Table S4, S7, and S8).

Secondary outcomes

Secondary outcomes included 30-and 90-day mortality, length of stay (LOS), hospital charges, postoperative acute kidney injury (Supplement 1, section 5.1),[19] and pneumonia within 30 days (Supplement 1 and Table S4). In addition, we used postoperative wound infection as a negative control outcome as this would not be expected to be influenced by the anaesthesia type (Supplement 1, section 5.2). To study the secondary outcomes, we used logistic and negative binomial regression, respectively, using the raw exposure and adjusting for all confounding variables included in the primary analysis. In addition, we repeated these analyses in the propensity score-matched cohort.

The linearity assumption was tested using scatter plots. To adjust for non-linear relationships, continuous confounding variables were divided into quintiles or clinically relevant groups (Supplement 1, section 1.3). A two-sided *P*-value of <0.05 was considered statistically significant. Analyses were performed in Stata (StataCorp LP, version 13.0; StataCorp LLC, College Station, TX, USA).

Results

A total of 18 081 patients underwent ERCP under sedation or GA with intubation. Of these, 17 538 cases met the study criteria (Fig. 2). Sedation was used in 16 238 (92.6%) cases and GA was used in 1300 (7.4%) cases. Table 1 includes detailed patient characteristics and crude numbers of study outcomes. Details on drugs used in the two groups are provided in Table 2.

Primary analysis

In total, 938 (5.8%) cases experienced adverse discharge in the sedation group compared with 210 (16.2%) in the GA group. To address potential unmeasured confounding, we conducted an instrumental variable analysis among cases where the anaesthesiologist met the minimum caseload (n=17 414). A total of 389 anaesthesiologists were included, whose median overall caseload during the study period was 1778 cases (interquartile range, 1045–2560); 73.6% (12 819/17 414) of ERCPs were managed by a solo consultant anaesthesiologist. The adjusted mean predicted probability of using GA ranged from 0.2% to 63.2% across anaesthesiologists, which was dichotomised into low (<50th percent rank) *vs* high (>50th percent rank) preference for using GA to generate the instrument. *F*-statistics were 97.6, indicating a strong instrument. After applying the instrumental variable, confounding variables were well balanced between groups,[11] with 32 of 35 covariates having a standardised difference of <0.1 (Supplement 1 and Table S3). Instrumental variable analysis suggested an 8.6% risk increase in adverse discharge among patients who received GA compared with sedation (aRD 8.6%; 95% CI, 4.5–12.6%; Table 3).

Key secondary analysis

Adjusted risks of cardiovascular sedation-related adverse events were higher in GA patients compared with patients who received sedation (Supplement 1, section 3.2), and were associated with the primary outcome of adverse discharge (Supplement 1, section 3.3). Cardiovascular sedation related adverse events mediated between 18.1% (1.8–34.5%; any duration of MAP <65 mm Hg, use of vasopressors, or both) and 23.8% (3.9–43.7%; ≥3 min of MAP <55 mm Hg, use of vasopressors, or both) of the primary association between GA and adverse discharge (Table 4). Adjusted risks of respiratory sedation-related adverse events were higher in sedation patients (Supplement 1, section 3.2) and did not significantly affect the primary outcome (Supplement 1, section 3.3).

Sensitivity analyses

After propensity score estimation, 1248 patients undergoing GA were matched to 1248 patients undergoing sedation. All 35 covariates were balanced between the groups (Supplement 1, Table S6).

Of 2496 patients, 134 (10.7%) experienced adverse discharge in the sedation group compared with 199 (15.9%) in the GA group. Logistic regression analysis in this cohort showed that GA was associated with a 5.2% risk increase in adverse

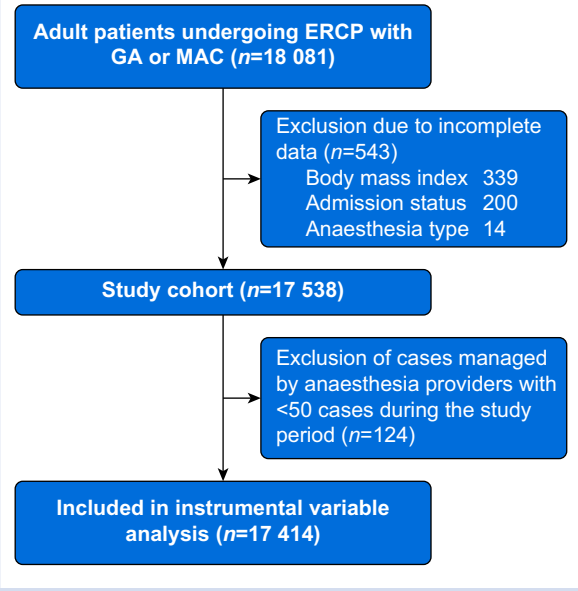

Fig 2. Study flow chart of patient selection depicting inclusion and exclusion criteria. GA, general anaesthesia MAC. monitored anaesthesia care; ERCP, endoscopic retrograde cholangiopancreatography.

Table 1 Patient characteristics across anaesthesia types. *Based on the raw exposure GA *vs* sedation/monitored anaesthesia care, 14 of 35 confounding variables that were included in the primary confounder model had a standardised difference of <0.1. †Data on intraoperative SpO_2 were available for 17 071 cases. Variables were expressed as mean (SD), median (IQR) or frequency (percentage). ASA, American Society of Anesthesiologists; IQR, inter-quartile range; LOS, length of stay; PRBC, packed red blood cells; RVU, relative value units; SD, standard deviation.

Total (*n*=17 538)	Monitored anaesthesia care (*n*=16 238)	General anaesthesia (*n*=1300)	Standardised difference of variables included in the primary confounder model*
Age (yr), median (IQR [range])	65 (53, 78 [18–103])	65 (52, 77 [20–104])	0.07
Sex, female, *n* (%)	8681 (53.5)	634 (48.8)	0.09
BMI (kg m^{-2}), mean (SD)	27.2 (5.98)	31.8 (9.7)	
Underweight, BMI <18.5 kg m^{-2}, *n* (%)	589 (3.6)	33 (2.5)	0.43
Overweight, BMI ≥30 kg m^{-2}, *n* (%)	4374 (26.9)	635 (48.8)	0.06
Federal insurance, *n* (%)	6891 (42.4)	655 (50.4)	0.16
Race/ethnicity, *n* (%)			0.10
Black	844 (5.2)	71 (5.5)	
Asian	522 (3.2)	27 (2.1)	
White	11 868 (73.1)	927 (71.3)	
Hispanic	520 (3.2)	41 (3.2)	
Other	2484 (15.3)	234 (18.0)	
ASA physical status, median (IQR)	3 (2, 3)	3 (3, 3)	
ASA physical status >2, *n* (%)	9818 (60.5)	1047 (80.5)	0.45
Admission type, *n* (%)			0.21
Elective	7643 (47.1)	419 (32.2)	
Non-elective	8595 (52.9)	881 (67.8)	
Outpatient, *n* (%)	7504 (46.2)	396 (30.5)	0.33
LOS before the procedure, *n* (%)			0.38
Same-day procedure	12 197 (75.1)	778 (59.8)	
1–2 days	3160 (19.5)	342 (26.3)	
3–7 days	543 (3.3)	78 (6.0)	
7 days	338 (2.1)	102 (7.8)	
Preoperative ICU admission, *n* (%)	655 (4.0)	252 (19.4)	0.49
Emergency, *n* (%)	2082 (12.8)	419 (32.2)	0.48
PRBC units transfused within 24 h before the procedure, *n* (%)			
0	16 144 (99.4)	1261 (97.0)	0.18
1	41 (0.3)	15 (1.2)	
≥2	53 (0.3)	24 (1.8)	
Comorbidities within 1 yr before the procedure, *n* (%)			
Myocardial infarction	791 (4.9)	67 (5.2)	−0.01
Atrial fibrillation	1068 (6.6)	131 (10.1)	−0.13
Congestive heart failure	1185 (7.3)	162 (12.5)	−0.17
Peripheral vascular disease	751 (4.6)	78 (6.0)	−0.06
Cerebrovascular disease	482 (3.0)	49 (3.8)	−0.04
Dementia	271 (1.7)	25 (1.9)	−0.02
Chronic obstructive pulmonary disease	2019 (12.4)	223 (17.2)	−0.13
Anaemia	3590 (22.1)	350 (26.9)	−0.11
Peptic ulcer disease	577 (3.6)	63 (4.8)	−0.06
Reflux	2763 (17)	185 (14.2)	0.08
Malignant disease	1176 (7.2)	109 (8.4)	0.04
Metastatic cancer	2977 (18.3)	240 (18.5)	−0.003
Diabetes mellitus with/without complications	2770 (17.1)	318 (24.5)	−0.18
Renal disease	1420 (8.7)	158 (12.2)	−0.11
Moderate to severe liver disease	806 (5)	97 (7.5)	−0.10
Smoking	901 (5.5)	63 (4.8)	0.03
Alcohol abuse	829 (5.1)	61 (4.7)	
Drug abuse	325 (2.0)	29 (2.2)	
Anxiety disorders	1248 (7.7)	105 (8.1)	
Sleep apnoea	420 (2.6)	84 (6.5)	0.19
Gastric outlet obstruction during index-stay	118 (0.7)	13 (1)	
Intraoperative data, *n* (%)			
Sphincterotomy	1316 (8.1)	100 (7.7)	0.02
Biliary stent insertion	2743 (16.9)	266 (20.5)	
Biliary stent exchange	2656 (16.4)	127 (9.8)	
Lithotripsy	84 (0.5)	8 (0.6)	
Patient positioning, *n* (%)			

Continued

Table 1 Continued

Total (*n*=17 538)	Monitored anaesthesia care (*n*=16 238)	General anaesthesia (*n*=1300)	Standardised difference of variables included in the primary confounder model*
Prone	12 687 (92.4)	181 (16.4)	
Supine	415 (3.0)	898 (81.3)	
Other (left lateral, right lateral, sitting)	629 (4.6)	25 (2.3)	
Duration of anaesthesia care in minutes, median (IQR)	42 (33, 55)	62 (49, 79)	1.07
Work RVU, median (IQR)	6.9 (6.0, 8.2)	6.9 (6, 8.2)	0.14
Overall amount of fluids in ml	418.3 (312.7)	579.0 (397.5)	0.47
Oral morphine equivalent of total opioid dose in mg	9.9 (672.0)	15.7 (18.6)	1.01
Conversions from sedation to GA, *n* (%)	259 (1.6)	0 (0)	
Study outcomes			
Adverse discharge, *n* (%)	938 (5.8)	210 (16.2)	
30-day mortality, *n* (%)	310 (1.9)	73 (5.6)	
90-day mortality, *n* (%)	675 (4.2)	118 (9.1)	
Hospital LOS in days, mean (SD)	3.9 (7.4)	8.5 (17.1)	
Postoperative pneumonia, *n* (%)	121 (0.7)	24 (1.8)	
Postoperative acute kidney injury, *n* (%)	530/7375 (7.2)	141/761 (18.5)	
Postoperative wound infection, *n* (%)	173 (1.1)	20 (1.5)	
Respiratory sedation-related adverse events†			
Intraoperative SpO_2 <90% in min, mean (SD)	3.0 (3.6)	4.0 (5.4)	
Intraoperative SpO_2 decrease by 3% of baseline in min, mean (SD)	0.7 (1.4)	0.8 (1.6)	
SpO_2 <90% for any period of time, *n* (%)	2513 (15.9)	241 (18.9)	
SpO_2 <90% for ≥3 min, *n* (%)	935 (5.9)	108 (8.5)	
Cardiovascular sedation-related adverse events			
Intraoperative hypotensive minutes of MAP <65 mm Hg in min, mean (SD)	1.0 (2.9)	4.3 (6.2)	
Use of vasopressors, *n* (%)	1193 (7.3)	574 (44.2)	
Any duration of hypotension event of MAP <65 mm Hg, vasopressor use, or both, *n* (%)	4371 (26.9)	945 (72.7)	
Hypotension event of MAP <65 mm Hg for ≥3 min, vasopressor use, or both, *n* (%)	2402 (14.8)	774 (59.5)	
Any duration of hypotension event of MAP <55 mm Hg, vasopressor use, or both, *n* (%)	1966 (12.1)	690 (53.1)	
Hypotension event of MAP <55 mm Hg for ≥3 min, vasopressor use, or both, *n* (%)	1351 (8.3)	603 (46.4)	

discharge (aRD 5.2%; 95% CI, 2.6%–7.9%) compared with sedation (Table 3).

Several sensitivity and subgroup analyses demonstrated robust results, which are detailed in Supplement 1 and Table S4, S7, and S8. Using interaction analyses, risk-related interaction terms did not modify the effect (Supplement 1, section 4.4).

Secondary outcomes

GA was associated with higher risks of 30 day mortality (aRD 1.4%, 95% CI 0.5–2.3%; PSM cohort: aRD 2.1%, 95% CI 0.4–3.7%) and 90 day mortality (aRD 1.7%, 95% CI 0.5–2.9%; PSM cohort: aRD 2.2%, 95% CI 0.2–4.3%).

Patients who received GA had longer LOS than those who received sedation (median LOS [IQR], 4 [1–9] *vs* 2 [1–4] days), which remained robust in the full cohort (incidence rate ratio [IRR], 1.09; 95% CI, 1.04–1.13) and in the PSM cohort (IRR, 1.14; 95% CI, 1.04–1.25). GA was associated with increased hospital charges in both the full cohort (IRR, 1.07; 95% CI, 1.02–1.14) and the PSM cohort (IRR, 1.28; 95% CI, 1.14–1.44). Use of GA was associated with an increased risk of postoperative acute kidney injury (aRD, 3.6%; 95% CI, 1.3–5.9%; *n*=8136; PSM cohort: aRD, 6.4%; 95% CI, 2.8–10.1%) and pneumonia in the full cohort (aRD 0.8%; 95% CI, 0.03–1.6%; PSM cohort: aRD, 0.6%; 95% CI, −0.3%–1.6%). Finally, the anaesthesia type was not associated with postoperative wound infection (aRD, −0.02%; 95% CI, −0.06%–0.56%; PSM cohort: aRD, 0.3%; 95% CI, −1.3%–0.6%).

Discussion

In this large cohort of more than 17 500 patients undergoing ERCP, we demonstrated higher risks of adverse discharge among patients who received GA with intubation compared with sedation. Individual provider preferences for the approach to anaesthesia during ERCP varied substantially, and

Table 2 Different drugs used intraoperatively for sedation *vs* general anaesthesia. *Oral morphine equivalent included intraoperative dose of meperidine, morphine, hydromorphone, fentanyl, and remifentanil. †Non-depolarising NMBAs included intraoperative dose of cisatracurium, rocuronium, pancuronium, or vecuronium. NMBA-specific effective dose 95 (ED_{95}) is defined as the median effective dose required to achieve a 95% reduction in maximal twitch response from the baseline. ‡Norepinephrine equivalent of vasopressor dose included dose of epinephrine, norepinephrine, and phenylephrine. Values were expressed as mean (SD) or frequency (percentage). ED_{95}, effective dose 95; NMBAs, neuromuscular blocking agents.

Total (*n*=17 538)	Sedation (*n*=16 238)	General anaesthesia (*n*=1300)
Fentanyl in μg	10.7 (102.9)	59.9 (69.8)
Use of fentanyl, *n* (%)	2050 (12.6)	707 (54.4)
Oral morphine equivalent of total opioid dose in mg*	9.9 (672.0)	15.7 (18.6)
Use of opioids, *n* (%)	2118 (13)	729 (56.1)
Ketamine in mg	8.4 (14.3)	2.9 (10.5)
Propofol in mg	411.1 (339.9)	256.3 (302.2)
Use of propofol, *n* (%)	15 892 (97.9)	1165 (89.6)
End-tidal minimum alveolar concentration of volatiles and nitrous oxide, age adjusted	0.01 (0.09)	0.67 (0.34)
Use of volatiles and nitrous oxide, *n* (%)	891 (5.5)	1198 (92.2)
ED_{95} of total non-depolarising NMBAs†	0.01 (0.13)	0.35 (0.81)
Use of non-depolarising NMBAs, *n* (%)	75 (0.5)	327 (25.2)
Succinylcholine in mg	1.23 (11.5)	92.5 (222.4)
Use of succinylcholine, *n* (%)	196 (1.2)	1094 (84.2)
Norepinephrine equivalent of vasopressor dose in mg‡	0 (0.09)	0.02 (0.27)
Use of vasopressors, *n* (%)	1193 (7.3)	574 (44.2)
Etomidate in mg	0.02 (0.60)	2.55 (9.50)
Use of etomidate, *n* (%)	22 (0.1)	176 (13.5)
Midazolam in mg	0.91 (1.31)	0.83 (1.19)
Use of midazolam, *n* (%)	6643 (40.9)	522 (40.2)
Overall amount of fluids in ml	418.3 (312.7)	579.0 (397.5)

Table 3 Association between the use of general anaesthesia *vs* sedation for endoscopic retrograde cholangiopancreatography (ERCP) and the primary outcome of adverse discharge across analyses. Adjusted absolute risk differences (aRD) and 95% confidence intervals (CI) in adverse discharge between patients who received GA *vs* sedation for ERCP. *For provider data analyses, only anaesthesia providers who performed a minimum of 50 anaesthetics at the hospital during the study period were included. Cases performed by providers who did not meet the minimum caseload were excluded (*n*=124).

Model	aRD (95% CI)	*P*	*n*
Unadjusted standard logistic regression analysis	10.4 (8.3–12.4)	<0.001	17 538
Adjusted standard logistic regression analysis	2.9 (1.4–4.3)	<0.001	17 538
Adjusted instrumental variable analysis	8.6 (4.5–12.6)	<0.001	17 414*
Propensity score matching analysis	5.2 (2.6–7.9)	<0.001	2496

our mediation analysis suggested that the higher risk of intraoperative hypotensive events among patients undergoing GA mediated about one-fourth of the effect on the adverse outcome.

An increasing number of patients with severe comorbidities undergo ERCPs.[3,20] Earlier studies supported the use of GA compared with conscious sedation as the sedation often was not sufficient, leading to premature procedure termination.[2,21] In these studies, procedures under conscious sedation were supervised by the endoscopist only. Anaesthesiologist-administered sedation during ERCP improves recovery times, quality of sedation, and the rate of complications.[2–5] In our study, sedation was managed by anaesthesia professionals in all patients.

In a recent RCT including 200 ERCP patients, sedation-related adverse events were compared between patients undergoing sedation *vs* GA.[9] In contrast to our study, patients who had an unstable airway, a gastric outlet obstruction, or underwent emergent ERCP were excluded. By using these criteria,[9] 32% of patients who received GA in our study would have been excluded. Our data may provide a more generalisable conclusion on the effect of anaesthesia type during ERCP.

A main concern for patients undergoing ERCP with sedation is hypoxaemia. In our study, the proportion of patients who were hypoxaemic under sedation was very similar to the findings reported by Smith and colleagues.[9] In contrast, in the RCT no events of hypoxaemia were observed among patients who received GA,[9] whereas we observed hypoxaemia in 18.9% of GA cases, which is likely a consequence of more liberal inclusion criteria in our study. We conclude based on our data that those brief intraoperative desaturations are not indicative

Table 4 Adjusted odds ratios with 95% confidence intervals and P-values obtained from multivariable-adjusted path mediation analysis of cardiovascular sedation-related adverse events as mediator variables in the primary association between use of general anaesthesia and adverse discharge. *Direct effect comparing odds for adverse discharge if everyone had received general anaesthesia *vs* odds for adverse discharge if everyone had received sedation, thereby fixing rates of cardiovascular sedation-related adverse events to the value they would have had during sedation. †Indirect effect assuming that every patient received general anaesthesia. We compare odds for adverse discharge when rates of cardiovascular sedation-related adverse events change from the value during general anaesthesia to the one during sedation. The indirect effect represents the mediated proportion¶ of the total effect‡ and indicates if and to which extent the effect of GA use on adverse discharge was mediated through hypotension. ¶Percentage mediation by sedation-related adverse events was calculated using the following formula: [ln(indirect effect)/ln(total effect)×100. §Binary mediator variable combining an intraoperative hypotension event (any duration/≥3 min of MAP <55/<65 mm Hg), use of vasopressors, or both.

Mediator	Crude numbers of sedation-related adverse events		Direct effect* (95% CI)	Indirect effect† (95% CI)	Total effect‡ (95% CI)	Mediated in %¶ (95% CI)
	Sedation, *n* (%) (*n*=16 238)	GA, *n* (%) (*n*=1300)				
MAP <65 mm Hg, vasopressor use, or both						
Any duration§	4371 (26.9)	945 (72.7)	1.51 (1.20–1.90)	1.10 (1.02–1.17)	1.66 (1.32–2.08)	18.1 (1.8–34.5)
Required minimum of ≥3 min§	2402 (14.8)	774 (59.5)	1.50 (1.21–1.86)	1.11 (1.03–1.19)	1.66 (1.35–2.05)	20.5 (3.0–38.1)
MAP <55 mm Hg, vasopressor use, or both						
Any duration§	1966 (12.1)	690 (53.1)	1.49 (1.18–1.88)	1.11 (1.03–1.19)	1.65 (1.32–2.08)	20.5 (2.6–38.3)
Required minimum of ≥3 min§	1351 (8.3)	603 (46.4)	1.47 (1.16–1.86)	1.13 (1.05–1.21)	1.66 (1.32–2.07)	23.8 (3.9–43.7)

of a poor outcome. There was no association between adverse discharge and hypoxaemia events in our study.

In contrast, formal mediation analysis indicated that the higher risk of hypotension among patients receiving GA contributed to the increased risk of adverse discharge. Thus, our study helps to understand the mechanisms by which GA worsens outcomes in patients undergoing ERCP. Hypotension is a common intraoperative event, and evidence has shown that even brief intraoperative hypotensive events of MAP below 60–70 mm Hg may lead to myocardial injury, renal failure, and death.[14,22,23] In a recent consensus statement on intraoperative blood pressure management of the Perioperative Quality Initiative, it has been recommended to maintain systolic arterial pressures above 100 mm Hg and MAP above 60–70 mm Hg.[14] Of note, one-third of intraoperative hypotension events occur between anaesthesia induction and surgical incision,[24] emphasising that the anaesthesia type is a key element of hypotension management. Future studies are needed to define best practices for intraoperative blood pressure management during ERCP.

In our study, hospital LOS in patients with GA was double that of patients with sedation, a finding that remained significant in adjusted analyses. This finding is supported by other studies comparing sedation vs GA in patients undergoing thyroidectomy,[25] breast surgery,[26] aortic valve replacement,[27] aortic aneurysm repair,[28] or hernia repair.[29] It would be important to evaluate if some of the mechanism leading to longer LOS and higher vulnerability to adverse discharge with GA compared with sedation can be prevented.

There are several important limitations to our study.

Patients who receive GA for ERCP may be generally sicker than those undergoing sedation. The two groups were similar with respect to age and BMI, and there were only small differences in ASA class. Patients who received GA were more often inpatients, and underwent longer and more emergent procedures than patients under sedation. To address confounding, we used an instrumental variable analysis as our primary analysis based on observed variability across anaesthesiologists in the use of GA *vs* sedation for ERCP. Our instrumental variable did achieve balance of most covariates across groups, which indicates validity of the instrument to reduce the risk of unmeasured confounders.[30] We used several sensitivity analyses to test the robustness of the instrumental variable analysis as an analytic approach, and propensity matching, and the similar results were confirmatory.[11,12] However, unmeasured confounders cannot be excluded. Further RCTs investigating the impact of GA use in the endoscopy setting are needed, and the results of our study may be helpful in determining the effect size of a larger study.[31,32]

Our institution is a highly specialised centre with a high volume of nearly 30 000 endoscopic procedures each year. Three out of four ERCP patients received anaesthesia care by a solo consultant anaesthesiologist. Given the high level of experience, we have optimised the use of sedation for most advanced endoscopic procedures such that sedation has become the default choice for ERCPs, and most sedation cases are conducted in prone position. In addition, we rarely use opioids and benzodiazepines but propofol sedation in the majority of sedation cases.

In summary, in this large cohort of patients undergoing ERCP, we demonstrated a higher risk of adverse discharge among patients who received GA with intubation compared with sedation. More hypotensive events among patients under GA partly contributed to this finding. There is marked provider-attributable variability in the choice of anaesthesia type for ERCP. Results of this study suggest that the use of sedation during ERCP facilitates less adverse discharge for patients in whom GA is not clearly indicated.

Authors' contributions

Study concept and design: FCA, AA, SDG, PS, XX, ES, MSS, ME
Acquisition, analysis, or interpretation of data: FCA, AA, SDG, PS, SN, TT, ME

Statistical analysis: FCA, AA, SDG, PS, XX, ME
Administrative, technical, or material support: XX, TMB, ES, MSS, ME
Study supervision: XX, ES, MSS, ME
Drafting of the manuscript: FCA, AA, ME
Critical revision of the manuscript for important intellectual content: FCA, AA, SDG, PS, SN, XX, TMB, ES, MSS, ME
All authors approved final version to be published and agreed to be accountable for all aspects of the work.

Declarations of interest

ME serves as a consultant on the advisory board of Merck & Co., holds equity in Calabash Bioscience Inc., and is an associate editor of the *British Journal of Anaesthesia*. The other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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